REMARKS

Claims 1 to 12 have been examined. Claims 1, 2, 4 to 7 and 9 to 12 have been amended. Support for the amendment to claim 1 is found, for example, in Examples 4 and 5 of the present specification. In these examples, patients who appeared not to have a renal disease were studied for a two-year period to establish a relationship between an elevated level of L-PGDS with an early stage of renal diseases. Amendments to claim 2 are based, for example, on Examples 6, 7, and 8 on pages 25 to 28. The remaining claims were amended to correct minor informalities. No new matter has been added.

New claims 13 to 20 have been added based on the existing claims and the specification. Specifically, claims 13 to 17 roughly correspond to claims 1 to 5, and claims 18 to 20 are based on Examples 1 to 9 on pages 18 to 31. Specifically, Examples 4, 5, and 9 provided evidence that individuals who were substantially asymptomatic of renal diseases but had an elevated L-PGDS concentration can develop renal diseases in subsequent years, thereby correlating a risk of developing renal diseases with elevated L-PGDS. No new matter has been added.

Claims 1 to 20 are pending.

Specification

The specification has been amended as stipulated in the office action.

Claim Objections

Objections to claims 5, 6 and 9 to 12 have been obviated by the amendments made to these claims herein.

Claim Rejections – 35 USC §112

Claims 2 and 4 to 12 have been rejected for not providing enablement for detection of a specific renal disease. That is, it is alleged that "the disclosure fails to state or teach one skilled in the art how to specifically use the L-PGDS concentration to detect a specific renal disease." However, Applicants submit that claims are enabling for the following reasons.

Amended claim 2 does not claim to detect or identify a specific renal disease. It claims a method of monitoring the progress of a renal disease by determining the concentration of L-PGDS in a fluid sample of a subject and evaluating the glomerular filtration activity of the subject. Nothing in the claim language indicates that the method is used to detect a specific renal disease. Claim 2 is enabled by the specification.

Claims 4, 5, 9 and 10 also do not claim to detect or identify a specific renal disease. As stated on page 1, lines 10 to 15, and page 12, line 19 to page 13, line 1, renal diseases cause glomerular lesions, and also renal diseases are caused by hypertension or lipid metabolic disorder. Such renal diseases among others are glomerulonephritis, nephrotic syndrome, diabetic nephropathy, polycystic kidney, and renal failure. That is, symptoms or patheogenesis are shared by many different renal diseases. Thus, no specific renal disease is being detected or identified. Claims 4, 5, 9, and 10 are enabled by the specification.

Furthermore, claim 8 having the same language as claim 3 does not claim to detect a specific renal disease. Claim 8 states that the concentration of L-PGDS is determined by an immunological assay method. There is no mention of detecting a specific renal disease. Claim 8 is enabled by the specification.

Claims 6, 7 and 11, 12 have been amended to depend on new claims 18 and 19, respectively, which state, "[a] method of determining whether an individual is at risk for a renal disease at an early stage of the renal disease...." The new claims do not claim to detect or identify a renal disease but rather claim to determine the risk of developing a renal disease by the concentration of L-PGDS in the body fluid sample. The specification provides sufficient support for determining this risk by correlating the high level of L-PGDS with the subsequent development of renal diseases (see Examples 1 to 9). Thus, amended claims 6, 7 and 11, 12 are fully enabled by the disclosure of the specification.

Thus, claims 2 and 4 to 10 are fully enabled for the foregoing reasons. Withdrawal of the §112 rejections is respectfully requested.

Claim Rejections - 35 USC §102

Claims 1 to 3 have been rejected as being anticipated by Hoffman et al. Applicants respectfully disagree for the following reasons.

Hoffman et al. discloses that the serum L-PGDS concentration in patients with end-stage renal failure increased as compared to the L-PGDS of the normal volunteers (see"Result" starting on page 500). Huffman et al. discloses that the various sera were purified by immunoaffinity chromatography, and the L-PGDS concentrations of the normal volunteers and dialysis patients were compared by the Western blot analysis (see Figs. 1 to 4 and page 500, column 2, lines 5 to 18). Furthermore, Huffman states that because of the high accumulation of L-PGDS in serum in pathological conditions, "it may become a much more reliable and sensitive parameter" "especially in early diagnosis of renal diseases or in following therapeutic treatments, e.g., renal transplantation..." (see page 505 lines 14 to 21).

Amended claim 1 recites:

> 1. (Amended) A method of detection of an early-stage renal disease, comprising:
>
> determining the concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample taken from a subject who substantially appears not to have any renal diseases; and
>
> comparing the determined concentration with a reference value set by determining the concentrations of human lipocalin-type prostaglandin D synthase in body fluid samples taken from healthy subjects.

As shown above, the present invention as claimed by claim 1 is directed to a method of detecting an early-stage renal disease of a subject who substantially appears not to have any renal diseases. In contrast, as indicated by the Examiner, Hoffman et al. discloses that the serum L-PGDS (β-TP) concentration in patients with **end-stage renal failure** increased as compared to the L-PGDS of the normal volunteers. Huffman et al.'s study demonstrates that a high level of L-PGDS correlates with end-stage renal failure; it does not show or disclose that a high level of L-PGDS correlates with the early-stage of a renal disease.

Although, Huffman et al. states that the use of L-PGDS may be a sensitive parameter for "early diagnosis of renal diseases," this is merely a speculation. It is clear that Huffman et al. at the time of publication did not possess the knowledge or evidence that early-stage renal disease correlated with a high level of L-PGDS. Thus, at least in this respect, the present invention as claimed and supported by examples 1 to 9 in the present specification is not anticipated by Huffman et al.

Claim 2 recites:

> 2. (Amended) A method of monitoring a progression of a renal disease. comprising:
> determining the concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample taken from a subject; and
> evaluating a glomerular filtration activity of the subject from the determined concentration.

Claim 2 as shown above is not anticipated by Huffman et al. because nowhere does Huffman et al. disclose "evaluating a glomerular filtration activity of the subject from the determined concentration." At least for the foregoing reason. claim 2 is not anticipated by Huffman et al.

Claim 3, which depends on claim 1, is not anticipated at least for the same reasons as claim 1.

Thus, for the foregoing reasons, claims 1 to 3 are not anticipated by Huffman et al. Applicant respectfully request that anticipation rejection be withdrawn.

New Claims

Claims 13 and 14 are not anticipated by Huffman et al. at least for the same reasons as claims 1 and 2, as theses claims have similar languages. Claims 15, 16 and 17, which correspond to claims 3, 4, and 5, respectively, are not anticipated by Huffman et al. at least for the same reasons as claims 3, 4, and 5.

Claims 18 to 20 are not anticipated by Huffman et al. at least for the same reasons as claim 1.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all pending claims be allowed. Enclosed is check for excess claim fees and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

Paragraph beginning at page 11, line 2 has been amended as follows:

In the present invention, it is possible to detect an early-stage renal disease in a subject by using as an indicator the L-PGDS concentration determined by the above-mentioned means. Also, it is possible to manage the disease state of a subject's renal disease by evaluating the glomerular filtration ability of the subject using as an indicator [or] the L-PGDS concentration determined by the above-mentioned means.

Paragraph beginning at page 16, line 28 has been amended as follows:

One hundred and ninety-two serum samples and 56 spotted urine samples were used. After these samples were appropriately diluted with the blocking solution, L-PGDS concentrations were determined by the sandwich ELISA as described above. The results of the assay revealed that the mean value± standard deviation of serum L-PGDS concentration obtained from healthy subjects was 0.848 ± 0.186 μg/ml. In the analysis [is] using spotted urine samples, the determined values were converted into urinary L-PGDS indexes (L-PGDS/g creatinine) using urinary creatinine concentrations, considering influences of the difference in urinary concentrations depending on the time of sampling. As a result, the mean value ± standard deviation of urinary L-PGDS index obtained from healthy subjects was 2.44 ± 1.86 mg/g creatinine. From the thus obtained mean value ± standard deviation, a [refence] reference value was set according to the formula described earlier, i.e. the mean value + (2 x standard deviation). The reference value for serum L-PGDS concentration was 1.22 μg/ml and the reference value for urinary L-PGDS index was 6.16 mg/g creatinine.

In the claims:

Claims 1, 2, 4 to 7 and 9 to 12 have been amended as follows (claims not amended are shown in bold, small face type for reference purposes only):

1. (Amended) A method of detection of an early-stage renal disease, comprising:

determining the concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample taken from a subject who substantially appears not to have any renal diseases; and

comparing the determined concentration with a reference value set by determining the concentrations of human lipocalin-type prostaglandin D synthase in body fluid samples taken from healthy subjects.

2. (Amended) A method of [disease state management for] monitoring a progression of a renal disease, comprising:

determining the concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample taken from a subject; and

evaluating [the] a glomerular filtration [ability] activity of the subject from the determined concentration.

3. The method of claim 1, wherein the determination of the concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample is performed by an immunological assay method.

4. (Amended) The method of any one of claims 1 to 3, wherein the renal disease [is accompanied with] causes glomerular lesions.

5. (Amended) The method of any one of claims 1 to 3, wherein the renal [diseases are associated with hypertensiton] disease is caused by hypertension or lipid metabolic disorder.

6. (Twice Amended) The method [of any one of claims 1 to 3] claim 18, wherein the renal [diseases are associated with hypertension or lipid metabolic disorder] disease comprises nephropathy.

7. (Amended) The method of [any one of claims 1 to 3] claim 18, wherein the renal disease [is] comprises glomerulonephritis, nephrotic syndrome, diabetic nephropathy, nephrosclerosis, polycystic kidney or renal failure.

8. The method of claim 2, wherein the determination of the concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample is performed by an immunological assay method.

9. (Amended) The method of [any one of claims] claim 8, wherein the renal disease [is accompanied with] causes glomerular lesions.

10. (Amended) The method of [any one of claims] claim 8, wherein the renal [diseases are associated with] disease is caused by hypertension or lipid metabolic disorder.

11. (Amended) The method of [any one of claims 8] claim 19, wherein the renal disease [is] comprises nephropathy.

12. (Amended) The method of [any one of claims 8] claim 19, wherein the renal disease [is] comprises glomerulonephritis, nephrotic syndrome, diabetic nephropathy, nephrosclerosis, polycystic kidney or renal failure.

13. (New) A method of detecting early-stage renal abnormality comprising:

determining a concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample of a subject who is substantially asymptomatic of renal diseases; and

comparing the concentration determined with a reference value set by determining the concentrations of human lipocalin-type prostaglandin D synthase in body fluid samples of healthy subjects.

14. (New) A method of monitoring a progression of renal abnormality comprising:

determining a concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample of a subject; and

correlating the determined concentration of human lipocalin-type prostaglandin D synthase with glomerular filtration function.

15. (New) The method of claim 13, wherein the determination of the concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample is performed by an immunological assay method.

16. (New) The method of any one of claims 13 to 15, wherein the renal abnomality causes glomerular lesions.

17. (New) The method of any one of claims 13 to 15, wherein the renal abnormality is caused by hypertension or lipid metabolic disorder.

18. (New) A method of determining whether an individual is at risk for a renal disease at an early stage of the renal disease, comprising:

determining a concentration of human lipocalin-type prostaglandin D synthase in a body fluid sample of a subject who is substantially asymptomatic of any renal diseases; and

comparing the concentration determined with a reference value set by determining the concentrations of human lipocalin-type prostaglandin D synthase in body fluid samples of healthy subjects, wherein the concentration is determined by enzyme-linked immunosorbent assay.

19. (New) A method of determining whether an individual is at risk for a renal disease at an early stage of the renal disease, comprising:

providing a body fluid sample of an individual who is substantially asymptomatic of any renal diseases; and

comparing the level of human lipocalin-type prostaglandin D synthase in the body fluid sample of the individual to the level of human lipocalin-type prostaglandin D synthase in a control sample from a healthy individual, wherein a higher level in the sample from the individual is an indication that the individual is at risk for developing a renal disease.

20. (New) A method of determining whether an individual is at risk for nephropathy at pre-nephropathic stage of the renal disease, comprising:

providing a body fluid sample of an individual who is substantially asymptomatic of any renal diseases; and

comparing the level of human lipocalin-type prostaglandin D synthase in the body fluid sample of the individual to the level of human lipocalin-type prostaglandin D synthase in a control sample from a healthy individual, wherein a higher level in the sample from the individual is an indication that the individual is at risk for developing a renal disease.